FINAL

DATA EVALUATION REPORT

Sodium Omadine

Study Type: Chronic Oral Toxicity in Nonrodents

Study Title: One Year Oral Toxicity Study in Cynomolgus Monkeys

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Work Assignment Number: 2-124
Clement Number: 393
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DATA EVALUATION REPORT

STUDY TYPE: Chronic Oral Toxicity in Nonrodents

MRID NUMBER: 411781-01

TOX CHEMICAL NUMBER: 790A

PC NUMBER: 088004

TEST MATERIAL: Sodium Omadine

SYNONYM: Sodium pyrithione; sodium-2-pyridinethiol-1-oxide

STUDY NUMBER: 397-047

SPONSOR: Olin Corporation, New Haven, Conn.

TESTING FACILITY: International Research and Development Corporation
Mattawan, Michigan

TITLE OF REPORT: One Year Oral Toxicity Study in Cynomolgus Monkeys

AUTHOR: Johnson, D.E.

REPORT ISSUED: April 14, 1989

EXECUTIVE SUMMARY: Sodium omadine was administered in water by gavage to groups of 5 male and 5 female cynomolgus monkeys for 1 year at dose levels of 0, 5, 25, or 150 mg/kg/day. The dose level of 150 mg/kg/day was lowered to 75 mg/kg/day at week 6 because of adverse effects on survival.

At 5 mg/kg/day decreased body weight gains were seen throughout the study in both sexes. At the higher doses emeses was observed in most animals and body weight gains were generally more severely depressed that at 5 mg/kg/day. At 75 mg/kg/day one male and one female died at weeks 13 and 35, respectively. *The cause of death* At 150 mg/kg/day one female was sacrificed in extremis at week 6. Clinical signs noted in the female that was sacrificed and in the female that died included prostration, decreased activity, emesis, thinness, weak appearance, and cold extremities. Emesis and ptyalism were seen in the male that died. Emesis was observed in most of the low-dose animals, and in all of the mid- and high-dose

were not apparent for either animal

animals. Hematological changes (i.e., decreases in red blood cell count, hemoglobin, and hematocrit levels) were slight and considered of minor toxicological importance.

The LEL of 5 mg/kg/day is based on decreased body weights. A NOEL was not determined.

CORE CLASSIFICATION: The study is Core Minimum and satisfies the minimal guideline requirements (83-1b) for a chronic oral study in non rodents. Food data consumption were not reported. These data would be useful since the body weight gain was affected.

A. MATERIALS, METHODS, AND RESULTS

1. Test Article Description

Name: Sodium omadine

Composition: 40% aqueous solution of sodium pyrithione

Batch number: IRDC 9180 and 9180B

Physical property: Amber liquid

Purity: 41.41% (Batch No. 9180)
40.5% (Batch No. 9180B)

Stability: Stable for at least 29 days when stored at room temperature

Storage: Room temperature in capped amber containers

2. Dosing Regimen: Monkeys were dosed by oral gavage for 7 days per week for at least 1 year with aqueous solutions of sodium omadine at 5, 25, or 150 mg/kg/day at a dosing volume of 1.0 ml/kg (followed by a rinse with 5 mL of deionized water). The high-dose of 150 mg/kg/day was reduced to 75 mg/kg/day on day 7 of study week 6 because of effects on survival. Vehicle controls received deionized water. Dosing solutions were corrected for the active ingredient. Doses were adjusted weekly based on the most recent body weight. Dosing solutions were prepared by diluting the stock solution weekly for weeks 1 through 5, and every 4 weeks thereafter.

3. Test Material Analyses for Purity and Stability

The stability of the test material in the dosing solutions prepared during week 1 was determined (by HPLC) from samples stored at room temperature for 0, 8, 15, and 29 days. The stability of the test material in the dosing solutions prepared during weeks 2, 3, 4, and 5 was determined from samples stored at room temperature for 0 and 8 days. Beginning at week 6, stability analyses of dosing solutions were performed every 4 weeks of the study from samples stored at room temperature for 0, 22, and/or 29 days.

TABLE 3. Mean Body Weight Gains (kg ± SD) of Monkeys Administered Sodium Omadine by Gavage for 1 Year[a]

Dose (mg/kg/day)	Mean Body Weight Gains at Selected Intervals		
	0-13 weeks	26-52 weeks	0-52 weeks
	Males		
0	0.02 ± 0.13	0.66 ± 0.46	0.96 ± 0.71
5	-0.18 ± 0.15	0.32 ± 0.23	0.32 ± 0.28
25	-0.22 ± 0.22	0.34 ± 0.11	0.18 ± 0.33
75	-0.05 ± 0.13	0.20 ± 0.14	0.15 ± 0.21
	Females		
0	-0.08 ± 0.13	0.12 ± 0.08	0.16 ± 0.13
5	-0.14 ± 0.05	0.10 ± 0.20	0.00 ± 0.20
25	-0.28 ± 0.22	0.14 ± 0.09	0.06 ± 0.18
75	-0.53 ± 0.39	0.07 ± 0.15	-0.17 ± 0.21

[a]Body weight gain data calculated by the reviewers from individual animal data

(a) Hematology

X	Hematocrit (HCT)*	X	Leukocyte differential count
X	Hemoglobin (HGB)*	X	Mean corpuscular HGB (MCH)
X	Leukocyte count (WBC)*	X	Mean corpuscular HGB concentration (MCHC)
X	Erythrocyte count (RBC)*	X	Mean corpuscular volume (MCV)
X	Platelet count*		Coagulation: activated partial thromboplastin time (APTT)
X	Reticulocyte count (RETIC)		Prothrombin time
	Red cell morphology		

* = Recommended by Subdivision F (November 1984) Guidelines

Note: Bone marrow smears were prepared from all monkeys. In order to confirm the absorption of test material additional blood was obtained from each animal at termination for determination of 2-methylsulfonylpyridine levels.

Results

Table 4 summarizes selected hematology data. Decreases in red blood cell count (14-18% in males; 13-20% in females), as well as hemoglobin (13-17% in males; 13-17% in females) and hematocrit (14-16% in males; 15-18% in females) levels were noted in the high-dose males and females when compared to controls; the decreases reached statistical significance ($p<0.05$ or $p<0.01$) at various study intervals. Decreases in red blood cell count (18-19% in males; 10-15% in females), and hemoglobin (13-17% in males; 11-14% in females) and hematocrit (12-17% in males; 10-13% in females) levels were also noted in the mid-dose animals; the decreases were statistically significant ($p<0.05$ or $p<0.01$) at various study intervals. Based on historical control data on red blood cell counts (provided in the study report), the decreases in red blood cell counts were within the normal range. In addition, there were no signs of hemolysis or changes in the cellularity in the bone marrow smears. Therefore, the hematological changes are considered to be of minor toxicological importance.

TABLE 4. Selected Hematology Parameters for Monkeys Administered Sodium Omadine by Gavage for 1 Year[a,b]

Parameter/ Month	Dose Groups (mg/kg/day)							
	Males				Females			
	0	5	25	150/75[c]	0	5	25	150/75[c]
Erythrocytes ($x10^6/mm^3$)								
0	6.68 ± 0.580	6.49 ± 0.305	6.27 ± 0.478	6.77 ± 0.418	6.30 ± 0.340	6.29 ± 0.444	6.17 ± 0.279	6.24 ± 0.276
1	6.69 ± 0.357	6.07 ± 0.557*	5.51 ± 0.247**	5.47 ± 0.229**	6.47 ± 0.136	5.70 ± 0.589*	5.50 ± 0.335**	5.18 ± 0.222**
3	5.89 ± 0.720	5.88 ± 0.216	5.14 ± 0.173	5.59 ± 0.353(4)[d]	5.97 ± 0.281	5.37 ± 0.346*	5.21 ± 0.209**	5.03 ± 0.335**(4)
6	6.54 ± 0.494	5.88 ± 0.197*	5.31 ± 0.158**	5.65 ± 0.292**(4)	6.08 ± 0.435	5.75 ± 0.324	5.47 ± 0.295*	5.32 ± 0.177**(4)
12	6.31 ± 0.355	5.77 ± 0.282*	5.12 ± 0.296**	5.46 ± 0.297**(4)	5.74 ± 0.136	5.32 ± 0.249	5.06 ± 0.378**	4.73 ± 0.133**(3)
Hemoglobin (g/dL)								
0	12.4 ± 0.45	12.3 ± 0.49	11.9 ± 0.59	13.2 ± 1.11	11.6 ± 0.86	12.0 ± 1.22	11.6 ± 0.50	12.0 ± 0.95
1	12.6 ± 0.65	11.9 ± 1.18	10.6 ± 0.65**	10.5 ± 0.82**	12.2 ± 0.82	11.2 ± 1.23	10.5 ± 0.25**	10.1 ± 0.61**
3	13.0 ± 0.71	13.1 ± 0.97	11.3 ± 0.60*	12.2 ± 1.05(4)	12.9 ± 1.00	12.0 ± 0.81	11.5 ± 0.42*	11.2 ± 0.93*(4)
6	12.7 ± 0.85	11.9 ± 0.91	10.6 ± 0.31**	11.0 ± 0.61*(4)	11.8 ± 1.18	11.8 ± 0.58	10.9 ± 0.40	11.0 ± 0.41(4)
12	12.7 ± 0.64	12.1 ± 0.79	10.7 ± 0.48**	11.1 ± 0.51**(4)	11.8 ± 0.82	11.3 ± 0.72	10.6 ± 0.61	10.0 ± 0.66*(3)
Hematocrit(%)								
0	42.8 ± 2.11	43.2 ± 1.69	41.6 ± 2.58	44.6 ± 3.44	40.9 ± 3.50	42.3 ± 3.88	40.2 ± 1.95	42.3 ± 2.98
1	45.6 ± 2.05	42.7 ± 3.79	38.9 ± 1.71**	38.5 ± 1.86**	44.5 ± 2.59	40.7 ± 3.95	38.6 ± 1.42**	36.7 ± 1.73**
3	42.0 ± 3.08	42.5 ± 2.56	37.0 ± 0.83*	39.5 ± 2.93(4)	42.3 ± 2.82	39.4 ± 2.75	37.6 ± 1.61*	35.7 ± 2.27**(4)
6	44.0 ± 2.52	41.1 ± 2.16	36.7 ± 1.38**	37.8 ± 1.34**(4)	41.0 ± 4.50	40.3 ± 2.33	37.7 ± 1.85	36.7 ± 1.20(4)
12	42.2 ± 1.59	40.1 ± 2.91	35.4 ± 1.67**	36.4 ± 1.98**(4)	38.6 ± 2.38	37.2 ± 2.14	34.7 ± 2.08*	32.8 ± 0.87**(3)

[a]Data extracted from Table 4, pages 64-68, study report
[b]Data based on 5 monkeys/sex/group unless otherwise indicated
[c]The dose of 150 mg/kg/day was administered through week 6; 75 mg/kg/day was administered thereafter
[d]Number in parenthese indicates number monkeys/sex/group

*Significantly different from control at $p<0.05$
**Significantly different from control at $p<0.01$

(b) Blood (clinical) chemistry

Electrolytes	Other
X Calcium*	X Albumin*
X Chloride*	Albumin/globulin ratio
Magnesium	X Blood creatinine*
X Phosphorus*	X Blood urea nitrogen*
X Potassium*	X Cholesterol*
X Sodium*	X Globulins
	X Glucose*
Enzymes	X Total bilirubin*
	Direct bilirubin
X Alkaline phosphatase (ALP)	X Total protein*
Cholinesterase	Protein electrophoresis
X Creatine phosphokinase	Phospholipid
Lactic acid dehydrogenase	Uric acid

X Serum alanine aminotransferase (SGPT)*
X Serum aspartate aminotransferase (SGOT)*
X Gamma glutamyltransferase (GGT)

* = Recommended by Subdivision F (November 1984) Guidelines

Results

There were no changes of toxicological significance in clinical chemistry parameters.

(c) Urinalysis

Urinalysis was performed on all monkeys/sex/group prior to treatment, and at months 1, 3, 6, and 12. The parameters checked (X) below were examined.

X Appearance*	X Sediment (microscopic)	X Bilirubin*
X Volume*	X Protein*	X Blood
X Specific gravity*	X Glucose*	X Nitrite
X pH*	X Ketones	X Urobilinogen

* = Recommended by Subdivision F (November 1984) Guidelines

Results

There were no changes of toxicological significance in urinalysis parameters.

5. Sacrifice and Pathology

Following 12 months of treatment, all surviving monkeys were sacrificed and necropsied. Animals that died during the study or that were sacrificed before the end of the study also received a complete gross examination. Tissues checked (X) below were examined

histologically. In addition, double-checked (XX) organs were weighed for monkeys sacrificed by design.

Digestive System	Cardiovascular/Hematologic	Neurologic
Tongue	X Aorta*	XX Brain*
X Salivary glands*	XX Heart*	X Peripheral nerve (sciatic nerve)*
X Esophagus*	X Bone marrow*	X Spinal cord* (three levels)
X Stomach*	X Lymph nodes*	XX Pituitary*
X Duodenum*	XX Spleen*	X Eyes (optic nerve)*
X Jejunum*	X Thymus*	
X Ileum*		Glandular
X Cecum*	Urogenital	
X Colon*		XX Adrenals*
X Rectum*	XX Kidneys*	Lacrimal gland
XX Liver*	X Urinary bladder*	X Mammary gland*
X Gallbladder*	XX Testes*	XX Thyroids*
X Pancreas*	X Epididymides	XX Parathyroids*
	X Prostate	Harderian glands
Respiratory	Seminal vesicle	
	XX Ovaries	
X Trachea*	X Uterus*	
X Lung*		
Larynx		

Other

X Bone (rib)*
X Skeletal muscle (thigh)*
X Skin*
X All gross lesions and masses*

* = Recommended by Subdivision F (November 1984) Guidelines

(a) Organ weights

There were no organ weight changes of biological importance. The increases in relative (to body) liver and kidney weights noted in treated males and females are ascribed to decreases in body weights. The increase in absolute adrenal weights in the high-dose females was not accompanied by pathological changes.

(b) Gross pathology

No gross lesions attributable to administration of sodium omadine were found.

(c) Microscopic pathology

There were no microscopic lesions attributed to administration of sodium omadine.

C. DISCUSSION

The design and conduct of the study were adequate. However, food consumption was not measured; food intake data may be useful in the interpretation of body weight gain changes observed in the treated animals. Measurements of the plasma levels of 2-methylsulfonyl-pyridine indicated that the test material was absorbed following oral administration.

One high-dose female administered 150 mg/kg/day sodium omadine by gavage for 6 weeks was sacrificed in extremis as the result of apparent toxicity; clinical signs noted prior to sacrifice included prostration, thinness, cold extremities, weak appearance, ptyalism, and emesis. Consequently, the 150-mg/kg/day dose level was reduced to 75 mg/kg/day at week 6. However, deaths occurred in one high-dose male (week 13) and one high-dose female (week 35). These results indicate that the administration of 150 mg/kg/day dose may have exceeded the maximum tolerated dose. The cause of the deaths in the monkeys was not ascertained. Clinical observations noted in the high-dose female that died at week 35 included prostration, decreased activity, emesis, thinness, and cold extremities. Moderate ptyalism and emesis were seen in the high-dose male that died at week 13.

Emesis was observed in the treated animals, and occurred within 15-30 minutes of dosing. The incidence of emesis was higher in the mid- and high-dose animals when compared to the low-dose animals. Also, the frequency of emesis was reported to be higher in the mid- and high-dose animals. Mean body weight gains were depressed in the low-, mid-, and high-dose monkeys at several intervals of the study. Moreover, the decreases in mean body weight gains were dose-dependent in the treated females at weeks 0-13 and 0-52. Hematological changes were slight and were considered of minor toxicological importance.

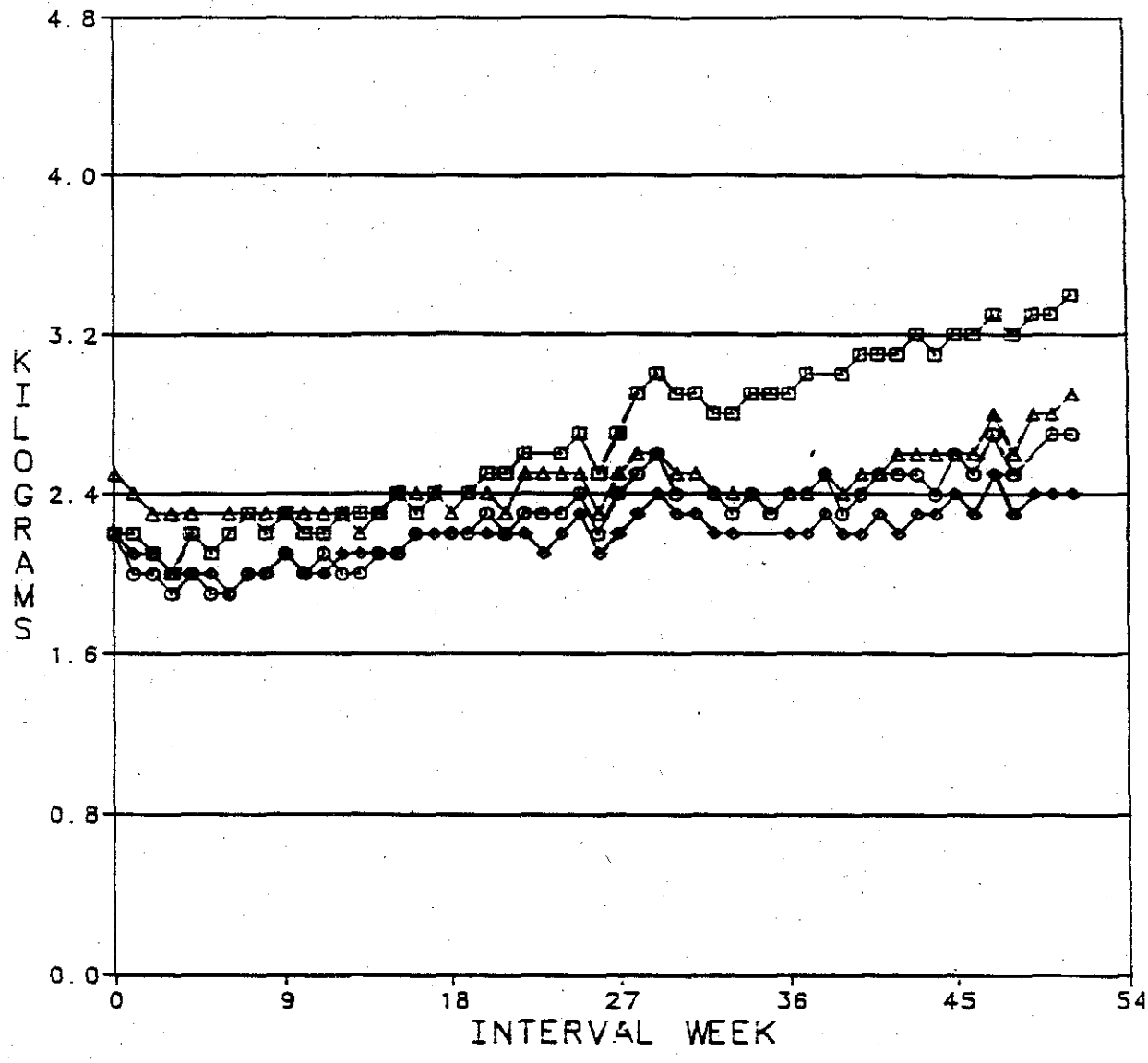
Hindlimb motor dysfunction and/or hindlimb muscle atrophy were observed in a subchronic oral study in rats (MRID # 407569-01), a subchronic inhalation study in rats (MRID # 411782-01), a chronic toxicity/oncogenicity study in rats (MRID # 421009-01), and in a 90-day dermal study in rats (MRID # 409362-01). These effects were not observed in the present study, indicating a possible species difference.

Based on decreases in body weight gains in the low-, mid-, and high-dose monkeys, the LOEL for systemic toxicity is 5 mg/kg/day. A NOEL for depressed body weight gain was not determined.

MEAN BODY WEIGHT

MALE

Figure 1



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Monkey Study

Figure 1 Cont.